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# Transcatheter Aortic Valve-in-Valve Implantation with Newer Generation Evolut Valve by Size of Failed Bioprosthesis

## ABSTRACT

**Background:** To evaluate the clinical outcomes of valve-in-valve transcatheter aortic valve replacement (ViV TAVR) with newer-generation self-expanding Evolut valves according to the size of the failed surgical bioprosthesis.

**Methods:** This single-center retrospective study evaluated consecutive patients undergoing ViV TAVR with the Evolut Pro/Pro+/Fx between 2018 and 2022. These patients were compared based on the true internal diameter (ID) of the failed bioprosthesis, specifically ≤19 mm (small group) vs. >19 mm (large group). The primary endpoint was a composite of all-cause mortality, stroke, myocardial infarction, and bioprosthetic valve failure. A Cox regression hazard model adjusted for covariates using propensity scores was used to assess the effect of the true ID on clinical outcomes.

**Results:** A total of 91 patients (small group, n = 35; large group, n = 56) were identified, and the median age of the entire cohort was 78 years. Patients in the small group were more likely to be female and have a small body surface area. The incidence of post-procedural mean gradient ≥20 mm Hg (40% vs. 8.9%, *P* = .001) and moderate/severe prosthesis-patient mismatch (63% vs. 38%, *P* < .001) was significantly higher in the small group. During a median follow-up period of 25 (range: 1.0-66) months, all-cause mortality showed no significant difference between the groups (adjusted *P* = .104); however, the rate of the primary composite outcome was significantly higher in the small group (adjusted hazard ratio 3.72, 95% CI 1.48; 9.37).

**Conclusion:** Valve-in-valve transcatheter aortic valve replacement for small bioprostheses was associated with worse early and mid-term outcomes compared with those for large bioprostheses.

**Keywords:** Aortic valve replacement, cardiac surgery, valve disease

## INTRODUCTION

Valve-in-valve (ViV) transcatheter aortic valve replacement (TAVR) has become a widely accepted procedure for the treatment of failed bioprostheses, with promising early and mid-term results[1-3] compared to redo surgical AVR (SAVR). However, there are concerns about the technical feasibility and the risk of significant post-procedural transvalvular pressure gradients after ViV TAVR, especially for small surgical bioprostheses.[4,5] However, the consequences of higher pressure gradients after ViV TAVR for small surgical bioprostheses compared to large bioprostheses remain controversial and sparse, especially with newer generation transcatheter heart valves.[4,6] Self-expanding valves have been shown to potentially outperform balloon-expandable valves in terms of lower post-procedural pressure gradients in small aortic annuli.[6,7] In line with these findings, we have been inclined to use self-expanding valves for small aortic annulus and ViV procedures, especially for small failed bioprosthetic valves. In this study, we compared early and mid-term outcomes of ViV TAVR with newer generation self-expanding valves according to the size of the failed surgical bioprosthesis.

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ORIGINAL INVESTIGATION

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## METHODS

### Patients and Methods

In this retrospective observational study, we reviewed the data of patients who underwent TAVR procedure at our institution between January 2018 and December 2022. Inclusion criteria were patients who underwent ViV TAVR with newer generation self-expanding valves (Evolut Pro/Pro+/Fx [Medtronic, Minneapolis, MN, USA]) for failed surgical bioprostheses at our institution. During the study period, 1170 TAVR procedures were performed and 91 patients qualified for our study. We excluded cases with TAVR for native aortic valve disease (n = 1050), ViV TAVR with balloon-expandable valves (n = 15), ViV TAVR with older generation self-expanding valves (n = 8), ViV TAVR for failed transcatheter heart valves (n = 5), and one case in which the procedure was aborted due to unsuccessful delivery of the transcatheter heart valve. We set these inclusion criteria to reflect the outcomes of current practice by focusing on newer generation valves. Additionally, because we predominantly use self-expanding valves for ViV TAVR, especially for small failed bioprostheses, we aimed to eliminate the selection bias between balloon-expandable and self-expanding valves, allowing us to clarify the ViV outcomes specific to self-expanding valves.

Patients were stratified according to the true internal diameter (ID) of the surgically implanted bioprosthetic valve (true ID ≤19 mm: small group and >19 mm: large group). The primary endpoint was a composite of all-cause mortality, all stroke, myocardial infarction, and bioprosthetic valve failure (primary composite outcome). Other endpoints of interest included a composite of all-cause mortality, all stroke, myocardial infarction, bioprosthetic valve failure, and rehospitalization for heart failure (secondary composite outcome) and all-cause mortality. Definitions, terminology, and presented outcomes were consistent with the Society of Thoracic Surgeons (STS)/American College of Cardiology Transcatheter Valve Therapy Registry and the Valve Academic Research Consortium 3 criteria.[8] The decision for ViV TAVR was made by a dedicated heart team, including cardiac surgeons, interventional and non-interventional cardiologists, and anesthesiologists, and was primarily based on surgical risk according to the STS of Predicted Risk of Mortality (STS-PROM), as well as patient anatomy and patient-specific factors such as frailty. Artificial intelligence-assisted technologies (such as Large Language Models, chatbots, or image creators) were not used in the production of the submitted work in this study.

### Statistical Analysis

The Shapiro–Wilk test was used to assess the distribution of continuous values, and depending on the distribution, continuous values are presented as mean ± SD or median (interquartile range). For comparisons between the 2 groups, the *t*-test was used for normally distributed continuous values, and the *U*-test was used for non-normally distributed values. Categorical values are reported as number (%), and the chi-square test or Fisher's exact test was used to compare the groups as appropriate. Kaplan–Meier curves with log-rank *P* values were constructed to estimate the cumulative incidence of events (a composite of all-cause mortality, stroke, myocardial infarction, and bioprosthetic valve failure, a composite of all-cause mortality, stroke, myocardial infarction, bioprosthetic valve failure, and rehospitalization for heart failure, and all-cause mortality) for each group. In addition, univariate and multiple Cox regression models were used to evaluate the effect of true ID (small or large) on late clinical outcomes. To avoid overfitting in the multiple model due to the inclusion of a large number of covariates relative to the number of events, we first calculated the propensity score for covariate adjustment. Subsequently, only 2 variables, true luminal diameter (small or large) and propensity score, were included in the multiple models.[9,10] The variables included in the propensity score calculation were age, sex, body surface area, STS-PROM, mode of surgically implanted bioprosthetic valve failure (stenosis, regurgitation, or combined), left ventricular ejection fraction, and transaortic mean gradient. For potentially important factors, the effects of true ID indexed to body surface area (indexed true ID as a continuous value), externally mounted leaflet valves (Trifecta [Abbott, Abbott Park, IL, USA] or Mitroflow [Sorin Group USA, Arvada, CO, USA]), and stentless valves, were also evaluated. All *P* values were 2-sided and a 5% level was considered significant. All analyses were conducted using the R software, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

## HIGHLIGHTS

- Clinical outcomes of transcatheter aortic valve-in-valve implantation with the newer generation Evolut valves according to the size of the failed surgical bioprosthesis.
- Higher incidence of the composite outcome of mortality, stroke, myocardial infarction, and bioprosthetic valve failure in patients with small failed bioprostheses.
- Implications for alternative strategies such as redo surgical replacement or aortic root enlargement at initial replacement in younger, lower-risk patients with a small annulus.

## RESULTS

### Baseline Patient Characteristics

Baseline patient characteristics are shown in Table 1. The median age for the entire cohort was 78 years, and the mode of failure of the surgically implanted bioprosthesis was 55% for stenosis, 26% for regurgitation, and 19% for a combination of stenosis and regurgitation. There were 35 and 56 patients in the small and large true ID groups, respectively. Notably, patients in the small ID group were predominantly female, and had a smaller body surface area, and were at a higher risk for STS-PROM. Indexed true ID was higher in the large group, but not statistically significant. Stentless valves were observed in 0 patients in the small group and 5 patients (8.9%) in the large group (*P* = .152); externally mounted leaflet valves were observed in 21 patients (60%) in the small group and 17 patients (30%) in the large group (*P* = .008).

**Table 1. Baseline Patient Characteristics**

| | True ID ≤ 19 mm | True ID > 19 mm | |
|---|---|---|---|
| | n = 35 | n = 56 | *P* |
| Age, years | 81 (74-85) | 77 (72-84) | .080 |
| Female | 26 (75) | 11 (20) | **<.001** |
| BSA, $m^2$ | 1.8 ± 0.2 | 2.1 ± 0.3 | **<.001** |
| BMI ≥ 30 $kg/m^2$ | 9 (26) | 25 (45) | .111 |
| NYHA III/IV | 20 (57) | 36 (64) | .646 |
| STS-PROM score | 5.3 (2.5-9.6) | 3.7 (2.5-6.0) | **.004** |
| Diabetes | 15 (43) | 17 (30) | .323 |
| Chronic lung disease | 12 (31) | 11 (21) | .412 |
| Creatinine, mg/dL | 1.2 (1.0-2.1) | 1.2 (1.0-1.5) | >.999 |
| Dialysis | 1 (2.9) | 3 (5.4) | >.999 |
| Cerebrovascular disease | 5 (14) | 7 (13) | >.999 |
| Peripheral artery disease | 8 (23) | 10 (18) | .755 |
| Prior PCI | 11 (31) | 18 (32) | >.999 |
| Prior CABG | 14 (40) | 25 (45) | .828 |
| Atrial fibrillation | 20 (57) | 19 (34) | .051 |
| Prior pacemaker/defibrillator | 6 (17) | 7 (13) | .758 |
| Native aortic valve disease | | | .818 |
| Stenosis | 21 (60) | 31 (55) | |
| Regurgitation | 1 (2.9) | 5 (8.9) | |
| Combined | 7 (20) | 11 (20) | |
| Endocarditis | 6 (17) | 9 (16) | |
| Implanted bioprosthesis | | | |
| Stented | | | |
| CE perimount/magna | 11 (21 mm) | 10 (23 mm), 19 (25-29 mm) | |
| Epic | 2 (21 mm) | 4 (23 mm) | |
| Hancock II | 0 | 1 (27 mm) | |
| Mitroflow | 2 (21 mm), 5 (23 mm) | 2 (25 mm) | |
| Mosaic | 1 (23 mm) | 0 | |
| Trifecta | 3 (19 mm), 11 (21 mm) | 12 (23 mm), 3 (25/27 mm) | |
| Stentless | | | |
| ATS 3f | 0 | 1 (23 mm) | |
| Freestyle | 0 | 3 (25/27 mm) | |
| Prima | 0 | 1 (23 mm) | |
| Indexed true ID*, $mm/m^2$ | 10.4 ± 1.2 | 10.9 ± 1.4 | .105 |
| Mode of bioprosthesis failure | | | .183 |
| Stenosis | 20 (57) | 30 (54) | |
| Regurgitation | 6 (17) | 18 (32) | |
| Combined | 9 (26) | 8 (14) | |
| LVEF, % | 65 (56-67) | 58 (53-65) | .140 |
| Mean gradient, mm Hg | 38 ± 14 | 33 ± 14 | .135 |
| Indexed AVA*, $cm^2/m^2$ | 0.45 (0.36-0.55) | 0.48 (0.40-0.72) | .063 |
| MR ≥ moderate | 8 (23) | 11 (20) | .919 |

Mean ± SD, median (interquartile range), or number (%).AVA, aortic valve area; BMI, body mass index; BSA, body surface area; CABG, coronary artery bypass grafting; CE, Carpenter-Edwards; ID, internal diameter; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; PC, percutaneous coronary intervention; STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality. *Indexed to BSA. Values in bold indicate statistical significance.

### Procedural Characteristics and Periprocedural Outcomes

The procedural characteristics and periprocedural outcomes are summarized in Table 2. All patients except 2 in the large group underwent transfemoral ViV TAVR (98%). Post-balloon dilatation was performed in 83% and 64% of patients in the small and large true ID groups, respectively; high-pressure inflation was used in 17% and 7.1% of patients in the small and large groups, respectively. One coronary obstruction

**Table 2. Procedural Characteristics and Periprocedural Outcomes**

| | True ID ≤ 19 mm n = 35 | True ID > 19 mm n = 56 | *P* |
|---|---|---|---|
| **Procedural characteristics** | | | |
| Urgent/emergent | 11 (31) | 16 (29) | .957 |
| Transfemoral access | 35 (100) | 54 (96) | .521 |
| Pre balloon dilatation | 1 (2.9) | 1 (1.8) | >.999 |
| Post-balloon dilatation | 29 (83) | 36 (64) | .095 |
| High-pressure inflation | 6 (17) | 4 (7.1) | .175 |
| Snorkel stenting | 4 (11) | 1 (1.8) | .070 |
| Evolut valve size | | | **<.001** |
| 23 mm | 34 (97) | 3 (5.4) | |
| 26 mm | 1 (2.9) | 37 (66) | |
| 29 mm | 0 | 15 (27) | |
| 34 mm | 0 | 1 (1.8) | |
| **Periprocedural outcomes** | | | |
| Periprocedural mortality | 0 | 0 | NA |
| Major cardiac structural complication | 1 (2.9) | 0 | .385 |
| Major vascular complication | 0 | 0 | NA |
| Need for second valve | 1 (2.9) | 1 (1.8) | >.999 |
| Acute stroke | 1 (2.9) | 2 (3.6) | >.999 |
| New permanent pacemaker implantation* | 3/29 (10) | 3/49 (6.1) | .665 |
| Mean gradient, mm Hg* | 17 (13-23) | 12 (8.0-14) | **<.001** |
| Mean gradient ≥20 mm Hg* | 14 (40) | 5 (8.9) | **.001** |
| **Prosthesis-patient mismatch** | | | **<.001** |
| Moderate | 16 (46) | 16 (29) | |
| Severe | 13 (37) | 5 (8.9) | |
| **Aortic regurgitation*** | | | .510 |
| Mild | 4 (11) | 8 (14) | |
| ≥Moderate | 1 (2.9) | 0 | |

Number (%); ID, internal diameter; NA, not applicable. *30-day data or in-hospital data if 30-day data is not available. Values in bold indicate statistical significance.

occurred in the small group, but periprocedural mortality was 0% in both groups. The incidence of post-procedural mean gradient ≥20 mm Hg and moderate/severe prosthesis-patient mismatch was significantly higher in the small group.

### Mid-term Outcomes

A total of 20 all-cause deaths (9 in the small ID group and 11 in the large ID group) were observed during a median follow-up period of 25 (range: 1.0-65) months with 1- and 2-year survival rates of 91% and 83%, respectively. All-cause mortality showed no significant difference between the groups (log-rank *P* = .073). In the small group, all strokes, myocardial infarctions, and bioprosthetic valve failures were observed in 4, 0, and 4 patients, respectively; in the large group, all strokes, myocardial infarctions, and bioprosthetic valve failures were observed in 3, 2, and 2 patients, respectively. As a result, the incidence of the primary composite outcome was significantly higher in the small ID group (log-rank *P* = .034). Figure 1 shows Kaplan–Meier curves for the primary and secondary composite outcomes and all-cause mortality. Supplementary Figure 1 shows Kaplan–Meier curves with log-rank *P* values for each component of the composite outcome (except all-cause mortality). At 1-year follow-up, the mean transaortic gradient remained significantly higher in the small ID group (17 [13-23] mm Hg, n = 22) compared to the large group (12 [8.0-14] mm Hg, n = 43). In the propensity score-adjusted regression analysis, although all-cause mortality was not significantly associated with true ID ≤ 19 mm, both primary and secondary outcomes were significantly associated with true ID ≤ 19 mm (Table 3). Neither indexed true ID, externally mounted leaflet valve, nor stentless valve was associated with composite outcomes or all-cause mortality (Supplementary Table 1).

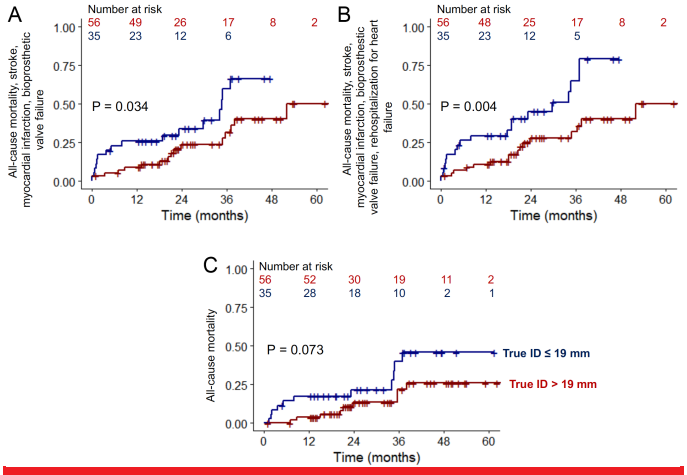


**Figure 1. Kaplan–Meier curves for (A) a composite of all-cause mortality, stroke, myocardial infarction, and bioprosthetic valve failure, (B) a composite of all-cause mortality, stroke, myocardial infarction, bioprosthetic valve failure, and rehospitalization for heart failure, and (C) all-cause mortality. ID, internal diameter.**

## DISCUSSION

The major findings of this study are as follows: 1) Patients undergoing ViV TAVR with the newer generation Evolut valves (Pro/Pro+/FX) for small bioprostheses (true ID ≤ 19 mm) were more likely to be female, and have a smaller body surface area and higher STS-PROM scores compared to those for large bioprostheses (true ID > 19 mm); 2) ViV TAVR for small bioprostheses was significantly associated with a higher post-procedural transaortic pressure gradient and a higher incidence of mean gradient ≥ 20 mm Hg and moderate/severe prosthesis-patient mismatch; and 3) was associated with worse mid-term composite outcomes of all-cause mortality, all stroke, myocardial infarction, and bioprosthetic valve failure ± rehospitalization for heart failure. Our 1-year

**Table 3. Results of Cox Regression Hazard Analysis for Late Outcomes**

| | Univariate | | Propensity Score Adjusted | |
|---|---|---|---|---|
| | HR [95% CI] | *P* | HR [95% CI] | *P* |
| All-cause mortality, stroke, myocardial infarction, and bioprosthetic valve failure | | | | |
| True ID ≤ 19 mm | 2.16 [1.06; 4.39] | .034 | 3.72 [1.48; 9.37] | .005 |
| All-cause mortality, stroke, myocardial infarction, bioprosthetic valve failure, and rehospitalization for heart failure | | | | |
| True ID ≤ 19 mm | 2.58 [1.32; 5.05] | .006 | 3.82 [1.60; 9.13] | .002 |
| All-cause mortality | | | | |
| True ID ≤ 19 mm | 2.24 [0.93; 5.41] | .073 | 2.50 [0.83; 7.53] | .104 |

HR, hazard ratio; ID, internal diameter.

and 2-year survival rates of 92% and 84% are consistent with previous studies.[11,12]

The post-procedural residual pressure gradient is a well-known problem after ViV TAVR especially for small bioprostheses.[4,5,13] However, the consequences of the residual pressure gradient on late outcomes remain unclear. Pingpoh et al[4] reported that, although ViV for small true ID bioprostheses ≤ 20 mm was associated with comparable mid-term mortality compared with implantation of larger bioprostheses, hospital readmission rates were significantly higher in the smaller bioprosthesis group. In the PARTNER 2 Aortic ViV Registry,[1] a composite of all-cause death and stroke was not associated with the size of the prior surgical bioprosthesis; however, there was a significant difference in the composite outcome between the 23 mm (Edwards Lifesciences, Irvine, CA, USA) and 26 mm Sapien valves during the 5-year follow-up. We stratified patients based on the true ID of the failed bioprosthetic valves, using >19 mm and ≤19 mm as the cut-off for large and small bioprostheses, respectively. This cut-off was chosen based on prior studies and clinical relevance, though there is no universally accepted definition for small bioprostheses. Many studies classify bioprosthesis sizes of ≥23 mm (true ID ≥21 mm or >20 mm) as large, and those ≤21 mm (true ID ≤19 mm or <21 mm) as small.[4,5,13] We opted for the lower threshold of true ID ≤19 mm to highlight the impact of small bioprostheses. As a result, our study examining the ViV TAVR outcomes with the newer generation Evolut valve showed that although all-cause mortality did not show a significant difference in all-cause mortality in either univariate or propensity score-adjusted analysis between the true ID ≤19 mm and >19 mm groups, significantly worse mid-term composite clinical outcomes were observed. One concern may be that the rate of patients undergoing high-pressure inflation during the ViV procedure was 11% in the present study, which is lower than the recent report of 21% of attempted bioprosthetic valve fractures from the STS/American College of Cardiology Transcatheter Valve Therapy Registry.[11] However, our mean post-ViV mean gradient with a median of 13 mm Hg in the overall cohort is consistent with previous studies,[11,12] and the safety and efficacy of this procedure remains controversial with a potential risk of increased in-hospital mortality and significant bleeding.[11] In addition, given that previous studies have suggested the safety and efficacy of direct TAVR for native severe aortic stenosis without predilation,[14] we primarily adopt a direct TAVR strategy in ViV TAVR as well. As a result, our predilation rate is lower compared to previous ViV TAVR studies, such as 7.1% reported by Rodés-Cabau et al[6] and 4.5% reported by Nikolayevska et al.[13] The role of balloon valvuloplasty in ViV TAVR remains an area that requires further investigation.

The use of TAVR procedures continues to grow, especially in younger and lower-risk patients; however, we need to be aware of the potential adverse clinical outcomes of ViV TAVR, especially for small bioprostheses. Redo SAVR in such patients, or aortic root enlargement for initial SAVR in patients with a small annulus,[15] might be beneficial in younger and lower-risk cohorts. These considerations also warrant further investigation to better guide treatment decisions.

This study has several important limitations. First, this is a single-center retrospective study with a small cohort and a relatively short observation period. This raises concerns about the robustness of the results and the statistical power to detect other important factors. In addition, patient characteristics were heterogeneous between the small and large ID groups. Despite our best efforts to exclude confounding factors by propensity score-adjusted analysis, the potential for unknown confounders remains. Although the cohort includes various types of failed bioprostheses, differences in outcomes based on the type of bioprosthesis were not examined in this study due to the limited number of the cohort. In addition, details of heart failure management or medications before and during follow-up were unclear, which may have influenced the results of this study. Given these limitations, a cautious interpretation of the results is warranted.

In conclusion, ViV TAVR is a safe and effective procedure with promising early- and mid-term outcomes. However, ViV TAVR for smaller bioprostheses was associated with worse early and mid-term outcomes compared to those for larger bioprostheses in terms of worse post-procedural hemodynamics and mid-term composite outcomes.

**Ethics Committee Approval:** The study protocol was approved by the Main Line Health Hospitals Institutional Review Board (IRB 45CFR164.512) on November 11, 2020.

**Informed Consent:** Individual patient consent was waived due to the retrospective nature of the study.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** Concept – B.R.; Design – S.S.; Supervision – W.A.G., S.M.G.; Resource – B.R.; Materials – S.M.G., W.A.G., B.R.; Data Collection and/or Processing – Y.Y., M.B., R.R., E.M.G., P.M.C.; Analysis and/or Interpretation – Y.Y., S.S., B.R.; Literature Search – E.M.G., P.M.C.; Writing – Y.Y.; Critical Review – W.A.G., S.M.G.

**Declaration of Interests:** B.R. is a consultant for Medtronic, Boston Scientific, AtriCure, Schockwave and Corcym. The other authors have no conflicts of interest to declare.

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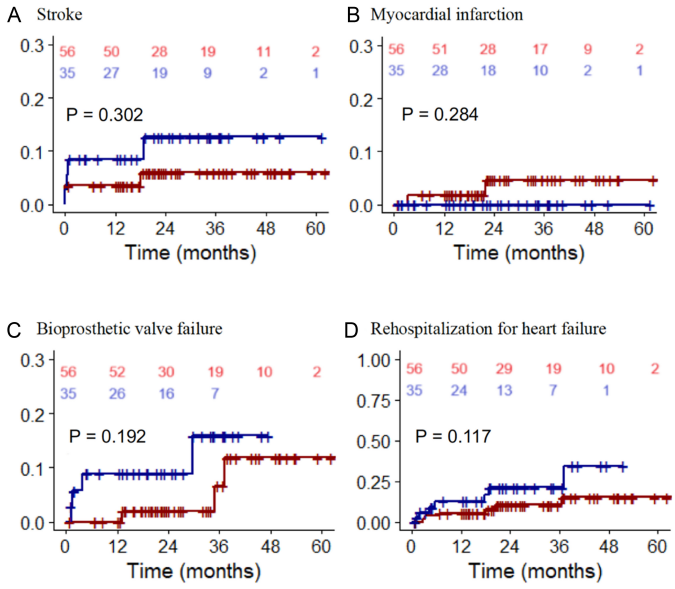


**Supplementary Figure 1. Kaplan-Meier curves with log-rank *P* values for (a) stroke, (b) myocardial infarction, (c) bioprosthetic valve failure, and (d) rehospitalization for heart failure between true internal diameter ≤ 19 mm (blue) and > 19 mm (red).**

**Supplementary Table 1. Results of Cox regression hazard analysis for late outcomes**

| | Primary composite* | Secondary composite** | All-cause mortality |
|---|---|---|---|
| | Hazard ratio [95% confidence interval] *P* value | | |
| Indexed true internal diameter | | | |
| Univariate | 0.80 [0.60; 1.05]<br>*P* = 0.101 | 0.92 [0.71; 1.19]<br>*P* = 0.518 | 1.01 [0.72; 1.37]<br>*P* = 0.968 |
| Propensity score adjusted | | Not applicable | |
| Externally mounted leaflet valve | | | |
| Univariate | 1.75 [0.87; 3.51]<br>*P* = 0.114 | 1.43 [0.75; 2.78]<br>*P* = 0.280 | 1.10 [0.46; 2.66]<br>*P* = 0.829 |
| Propensity score adjusted | 1.63 [0.76; 3.50]<br>*P* = 0.110 | 1.40 [0.68; 2.86]<br>*P* = 0.350 | 1.03 [0.40; 2.65]<br>*P* = 0.870 |
| Stentless valve | | | |
| Univariate | 0.94 [0.22; 3.97]<br>*P* = 0.937 | 1.03 [0.25; 4.32]<br>P = 0.967 | 0.81 [0.11; 6.07]<br>*P* = 0.839 |
| Propensity score adjusted | 0.66 [0.15; 2.95]<br>*P* = 0.937 | 0.79 [0.18; 3.59]<br>*P* = 0.820 | 1.09 [0.13; 8.91]<br>*P* = 0.969 |

*All-cause mortality, stroke, myocardial infarction, and bioprosthetic valve failure. **All-cause mortality, stroke, myocardial infarction, bioprosthetic valve failure, and rehospitalization for heart failure.